Remarks

Claims 1-12, 14-26, and 28-56 are pending. Claims 1, 3, 31, 32, 33, 46, and 50 are the independent claims.

I. Amendments to the Claims

Claims 1, 3, 31-33, 46, and 50 have been amended to specify that the pharmaceutical formulation is contained (i.e., stored) in a drug delivery device in a dry state. Support for these amendments may be found throughout the specification, including page 4, lines 15-23; page 5, line 20-page 6, line 2; page 26, lines 19-27; and page 33, line 26-page 34, line 10. The specification teaches dry powder inhalers (DPIs), which are pulmonary drug delivery devices containing a pharmaceutical formulation in a dry state. Claim 27 has accordingly been cancelled.

Claim 9 has been amended to depend upon claim 8, instead of claim 6. This amendment corrects an obvious typographical error.

No new matter has been introduced by any of these amendments.

II. Rejections Under 35 U.S.C. § 112

Claim 1 is rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Claim 9 is rejected under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as their invention. The rejections are respectfully traversed.

A. 35 U.S.C. § 112, First Paragraph

In order to reject a claim under 35 U.S.C. 112, first paragraph, an Examiner "must set forth express findings of fact regarding the . . . analysis which support[s] the lack of written description conclusion." M.P.E.P. § 2163. The conclusion should be supported by an analysis that "[e]stablish[es] a *prima facie* case by providing reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed." *Id.* (emphasis added). No "reasons" or "express findings of fact" are presented in the Office Action to justify the rejection.

Instead, the Examiner merely concludes that "[t]he claim(s) contains subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." (Office Action, page 2). This statement and the Examiner's unexplained conclusion that the "Applicant does not have support in the specification for the newly claimed limitation" fail to provide any "reasons" for the rejection or "express findings of fact" that support it. (*Id.*). Therefore, the "description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption." (M.P.E.P. § 2163). Without any facts to rebut the presumption, the rejection should be withdrawn.

Furthermore, "[t]he subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order to satisfy the description requirement." M.P.E.P. § 2163.02. That is, Applicants are not required to claim a feature precisely as disclosed in the specification.

The Examiner is unjustified in rejecting the claim merely because it is not a verbatim recitation of its description in the specification. The microparticle's claimed feature of "having voids defined by a structural material" is undeniably embraced by the specification.

First, the "matrix material" and "structural material" are explicitly defined in the specification. It describes that "[t]he porous microparticles comprise a matrix material and a pharmaceutical agent. . . [and] the term 'matrix' refers to a structure including one or more materials in which the pharmaceutical agent is dispersed, entrapped, or encapsulated." (Pg. 12, Lns. 15-19) (emphasis added). These sentences in the specification clearly define the "structural material" referred to in claim 1.

Second, the feature that the porous microparticles have "voids defined by" the structural material is clearly evident in the original description. "Voids" is a well-established term to which the Applicants do not impart any special meaning. A "void" is defined as "1: a: not occupied . . . b: not inhabited . . . 2: containing nothing <*void* space>." (Merriam-Webster's Online Dictionary). The specification is consistent with these common definitions.

Furthermore, Applicants' description of density measurements uses the term "voids" in a manner consistent with the well-established definition. The specification teaches that the volume of the solid material in the microparticles "excludes the volume of voids contained in the microparticles;" and the mass of the microparticles excludes the "mass of voids [which] is assumed to be negligible." (Pg. 9, Ln. 19 to Pg. 10, Ln. 10). Therefore, the "voids" do not contribute to the volume or mass of the particles, because they are unoccupied or uninhabited spaces that contain nothing. Therefore, the validity of these assumptions relies on the consonance between the Applicants' understanding of the term "voids" and the well-established definitions.

Because Applicants have adhered to the commonly-recognized definition of "voids," the Examiner's rejection is improper. Section 2163 of the M.P.E.P. clearly states that "[t]he absence of definitions or details for well-established terms or procedures should not be the basis of a rejection under 35 U.S.C. 112, para. 1, for lack of adequate written description."

The fact that Applicants considered the formation of "voids" in the microparticles when calculating microparticle densities illustrates that, as of the filing date, Applicants contemplated and were in possession of microparticles with "voids defined by the structural material." Accordingly, a person of skill in the art would realize, upon reading the specification as a whole, that Applicants indisputably were in possession of microparticles "having voids defined by a structural material."

Applicants respectfully submit that the specification supports the claim limitation "having voids defined by a structural material" and the rejection should be withdrawn.

B. 35 U.S.C. § 112, Second Paragraph

Claim 9 has been amended to depend upon claim 8, rather than claim 6. Claim 6 previously lacked a clear antecedent basis for the subject matter of claim 9. Claim 8, on the other hand, does, as it recites that the "pharmaceutical agent comprises a corticosteroid." Therefore, the limitation of amended claim 9 has sufficient antecedent basis. The rejection therefore is moot.

III. Rejection Under 35 U.S.C. § 102

Claims 1-10, 14-21, 25-27, and 31-53 are rejected under 35 U.S.C. § 102(a) as anticipated by U.S. Patent No. 6,309,623 to Weers et al. (hereinafter "Weers"). The rejection is respectfully traversed.

A. Applicants' Claimed Subject Matter

Applicants' amended claim 1 is specifically drawn to "dry powder sustained release pharmaceutical formulation for delivery to the lungs of a patient by inhalation." The inhaled formulation comprises "porous microparticles having voids defined by a structural material which comprises a pharmaceutical agent dispersed in a hydrophobic matrix material." The microparticles "have a geometric size between 0.1 μm and 5 μm and an average porosity between 15 % and 90 % by volume." These features, in combination with the matrix material, insure that a "therapeutically or prophylactically effective amount of the pharmaceutical agent is released from the microparticles in the lungs for" a desired amount of time after inhalation. The inhaled formulation is a dry powder that is contained in a drug delivery device in a dry state.

B. The Primary Reference, Weers

Weers discloses "stabilized dispersions for the delivery of a bioactive agent." These are *liquid* dispersions, not dry powder formulations. Weers does not disclose or suggest a dry powder formulation that is contained in a drug delivery device *in a dry state*.

Weers teaches that its microparticles are dispersed in a "continuous phase suspension medium." (Col. 5, Lns. 4-5). The "suspension medium comprises at least one propellant and substantially permeates said perforated microstructures." (Col. 4, Lns 51-53). Weers states that "suitable propellants for use in the **suspension mediums of the present invention** are those propellant gases that can be **liquefied** under pressure at room temperature." (Col. 5, Lns. 14-17) (emphasis added). Weers' microparticles therefore are stored in a liquefied propellant as a "stabilized dispersion." They are not contained in a drug delivery device in a *dry* state, as required by Applicants' claims.

The "stabilized dispersion" is created according to the technique disclosed in Weers' Examiner IX. Example IX discloses the preparation of metered dose inhalers ("MDIs") comprising "hollow porous particles prepared in Examples I, III, IV, V, VI, and VII" and propellant in a 10 mL aluminum can. Therefore, the particles of Examples V and VI, to which the Examiner refers in the Office Action, are combined with a propellant that is liquefied under pressure to form a "stabilized dispersion" prior to inhalation. The inhalation of the "white powder[s]" created in Examples V and VI is not described, because Weers does not teach, disclose, or suggest the inhalation of a dry powder formulation that is not dispersed within a "suspension medium" while in the drug delivery device.

Applicants' particles are not combined with a liquid propellant or other "suspension medium." Rather, they are in the form of a dry powder that is stored in a drug delivery device in a dry state. Accordingly, Applicants' claims are novel over Weers.

IV. Rejection Under 35 U.S.C. § 103

Claims 11, 12, 22-24, 28-30, and 54-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weers. The rejections are respectfully traversed.

Applicants' claims are not obvious from Weers, as Weers offers no "suggestion or motivation . . . to one of ordinary skill in the art, to modify the reference" to deduce Applicants' claims. (M.P.E.P. § 2143). Weers teaches away from particles contained in a device in a dry state, such as those in a DPI.

A DPI is an inhaler that delivers the pharmaceutical formulation as a dry powder. The dry powder is stored in the DPI in a dry state; and, inhaled without the benefit of a propellant. In contrast, a metered dose inhaler (MDI) uses a liquid propellant. (*See* Weers Col. 1, Lns. 40-44).

An MDI, unlike a DPI, includes a suspension medium, such as a propellant, in which the pharmaceutical-containing particles are dispersed.

The stability of this dispersion is the focus of Weers. Weers teaches that "the present invention employs novel techniques to reduce attractive forces between the dispersed components and to reduce density differences, thereby retarding degradation of the disclosed dispersions by flocculation, sedimentation or creaming." (Col. 3, Ln. 63 to Col. 4, Ln. 2). "As such, the disclosed stable preparations facilitate uniform dose delivery by metered dose inhalers [MDIs], and allow for more concentrated dispersions." (Col. 4, Lns. 2-4). In contrast, Applicants' claimed particles are in a dry state, such that flocculation, sedimentation, and creaming are not relevant.

According to Weers, "the use of hollow and/or porous perforated microstructures that substantially reduce attractive molecular forces, such as van der Waals forces, which dominate prior art dispersion preparations" solve the problem with flocculation, sedimentation, and creaming (Col. 4, Lns. 5-8). "In particular, the use of perforated (or porous) microstructures or microparticulates that are permeated or filled by the surrounding fluid medium, or suspensions medium, significantly reduces disruptive attractive forces between the particles." (Col. 4, Lns. 8-14). In contrast, Applicants' claimed formulations have no suspension medium to permeate the particles.

Weers *teaches away* from Applicants' claims because it teaches that a suspension medium and the medium's permeation of dispersed microparticles are essential. (*See* Col. 4, Lns. 57-62). This is evidenced, for example, by Weers' statements that physical characteristics of the particles "make both the continuous and dispersed phases essentially indistinguishable" (Col. 9,

Lns. 41-43) and that in addition to lending stability to the "stabilized preparation," the microstructures' pores and voids also serve "an important role in the resulting aerosol properties upon activation of the MDI." (Col. 14, Lns. 21-23).

These advantages require a suspension medium. Therefore, Weers teaches that the pores and voids on the microstructures are advantageous only when employed in a "stabilized preparation" of a drug delivery device, such as an MDI. In such a device, the particles are contained in a liquefied "suspension medium," which, according to Weers, permeates the microparticles due to the various pores and voids. The pores and voids cannot provide this advantage when the microparticles are contained in a drug delivery device in a dry state, because there is no liquefied "suspension medium" to permeate the formulation. Accordingly, Weers would not motivate a person of skill in the art to employ porous microparticles outside of a suspension medium as a dry powder pharmaceutical formulation.

Therefore, Weers teaches away from DPIs, because the reference as a whole is directed toward the stability of "stabilized dispersions." Not surprisingly, DPIs, which do not require stabilized dispersions, are not addressed in Weers' examples. Instead, the examples focus exclusively on MDIs.

Example IV discloses the preparation of metered dose inhalers (MDIs) containing the hollow porous particles of examples I, III, IV, V, VI, and VIII. Examples X, XI, XII, XIII, XIV, XV, XVI, XVII, and XVIII each address Anderson cascade impactor results for various MDI formulations, the effect of powder porosity on MDI performance, or the sedimentation rates of particles in suspension mediums. Weers mentions in the background that dry powder inhalers

and nebulizers are conventional devices, but implicitly teaches that these have drawbacks[1] not solved by Weers' invention for MDIs. Weers does not teach or suggest that its porous microparticles could or should be used in a dry state, i.e., in the absence of a suspension medium.

Furthermore, Weers' fails to teach anything about how to engineer a porous microparticle that can release an effective amount of a pharmaceutical agent in the lungs for at least two hours. Although Weers mentions altering the "structural matrix components," it tells nothing about selecting and coordinating the pharmaceutical agent, geometric size, and average porosity to achieve the recited drug delivery profile. Weers does not teach or suggest these adjustments.

The Supreme Court held in *KSR v. Teleflex* that "[i]f a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 417 (2007). Weers fails to teach or suggest how to obtain the Applicants' claimed release profile by adjusting the combination of the pharmaceutical agent, matrix material, geometric size, and average porosity to control release rate. This failure is significant because "[t]o the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008)(quoting *KSR*, 558 U.S. at 420). There are a large number of potential solutions for obtaining a desired release profile, and Weers fails to provide any guidance for how to adjust the claimed combination of properties to obtain desirable results from a dry powder

[1] DPIs and their accompanying difficulties were known in the art. *See* Newman, S.P. et al., RESPIRATORY MEDICINE, Vol. 96 (2002) 293-304 ("Cohesion and static charge interfere with drug handling during manufacture and with inhaler filling, can reduce uniformity in metering individual doses, and can cause drug retention within the device."); and Feddah, M.R. et al., J. PHARM. PHARMACEUT. SCI., Vol. 3 (2000) 317-24.

pharmaceutical formulation comprising porous microparticles—particularly ones that are not dispersed within a suspension medium. Weers offers no guidance to one of ordinary skill in the art how to coordinate and adjust the pharmaceutical agent, matrix material, geometric size, and average porosity to obtain the claimed drug delivery profile.

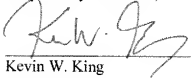
For all of the foregoing reasons, Applicants' claims are non-obvious over Weers.

V. Conclusions

Applicants respectfully submit that claims 1-12, 14-26, and 28-56 are patentable over the prior art of record. Allowance of all pending claims is therefore earnestly solicited.

The undersigned invites the Examiner to contact him by telephone (404.853.8068) if any outstanding issues can be resolved by conference or examiner's amendment.

Respectfully submitted,



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Date: September 18, 2009

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Attorney Docket No. 17976-0006 (ACU 115)